flow measurement of the carotid artery, myocardial and cerebral perfusion using fluorescent microspheres were performed during baseline (M1), sheath forwarding (M2), stent-graft deployment (M3) and after retraction of the sheath (M4) for evaluation of hemodynamic changes during transseptal deployment and concomitant myocardial and cerebral perfusion deficiency.
Results: Stent graft deployment into the ascending aorta was feasible in all six animals. Coronary arteries were patent in all cases confirmed by fluoroscopy. In four animals (66%) the innominate artery was partially occluded reflected by reduced carotid blood-flow. During advancing of the stent-graft transient hemodynamic instability due to severe mitral valve insufficiency occurred in all animals (M2, M3), after retrieval of the delivery-system (M4) hemodynamic stability recovered within ten minutes in all animals.
Conclusion: Transseptal access to the ascending aorta in a porcine model is feasible. Transient hemodynamic instability recovered to near preoperative values. Assessment of cerebral and myocardial perfusion for evaluation of the severity of the periprocedural deterioration using fluoresecent microspheres is under evaluation. Antegrade transseptal stentgraft deployment might be a promising tool.

TCT-452

Increased Endothelial Tetrahydrobiopterin Reduces In Stent Stenosis in Apolipoprotein E-Knockout Mice

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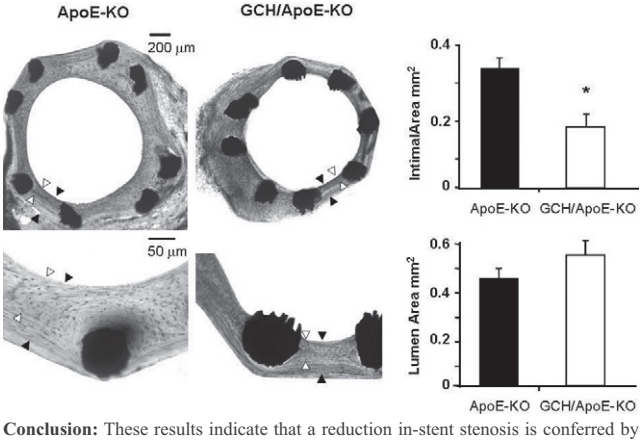
Background: In-stent stenosis, the principal cause PCI failure, is associated with reduced endothelial nitric oxide (NO) bioavailability. Tetrahydrobiopterin (BH4) is a required cofactor for NO synthesis by endothelial nitric oxide synthase (eNOS).
Methods: We investigated the importance of BH4 in regulating eNOS activity in in-stent stenosis using a transgenic mouse with endothelial overexpression of the rate-limiting enzyme in BH4 synthesis, GTP-cyclohydrolase I (GCH). Thoracic aortic segments which underwent balloon angioplasty and stenting from donor transgenic mice crossed onto ApoE-KO background (GCH-Tg/ApoE-KO) or their ApoE-KO littermates were grafted onto the carotid artery of isogenic recipients.
Results: Aortic BH4 levels were 8-fold higher in GCH-Tg/ApoE-KO mice compared to ApoE-KO controls (P<0.01). Despite equal stent expansion and injury scores, in-stent stenosis was reduced by 47% (P<0.001) in GCH-Tg/ApoE-KO mice. NO synthesis, measured using arginine to citrulline conversion and electron paramagnetic resonance in aorta of experimental animals, was not different between groups. However, O2- production was significantly attenuated in GCH-Tg/ApoE-KO mice measured on both aortic sections using oxidative confocal microtopography and whole aorta by lucigenin enhanced chemiluminescence. eNOS inhibition by L-NAME reversed these effects indicating that under basal conditions GCH-Tg/ApoE-KO mice had preserved eNOS coupling promoting NO synthesis.



Conclusion: These results indicate that a reduction in-stent stenosis is conferred by maintaining eNOS coupling and reducing O2- production. These findings highlight the importance of eNOS function in in-stent stenosis.

TCT-453

Early Enzymatic Infarct Size Assessment using Heart Specific Fatty Acid Binding Protein

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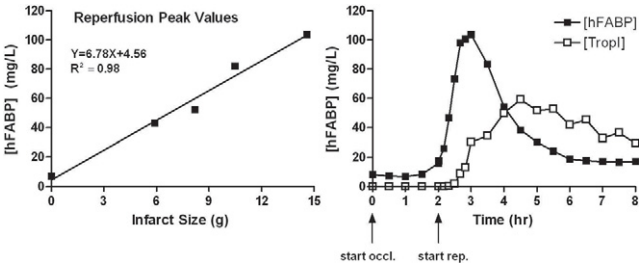
Background: In clinical practice, myocardial necrosis (MN) is determined by Troponin (Trop) which can be detected only several hours after onset of ischemia. In search for early specific and accurate biomarkers to determine MN and quantify infarct size (IS), we evaluated heart specific fatty acid binding protein (hFABP), a small cytosolic, cardiac specific marker released during acute myocardial infarction (AMI) ± reperfusion (R) in comparison to Trop and morphometric triphenyl tetrazolium chloride infarct size determination (TTC).
Methods: In 8 swine, AMI was induced by 8 hr chronic balloon occlusion (C) or 2 hr balloon occlusion followed by 6 hr reperfusion (R). Blood samples were taken at predetermined intervals and analyzed for hFABP and high sensitivity Troponin I (Trop I). TTC was used to determine IS.
Results: In AMI-C hFABP was detected faster than Trop upon occlusion (90±35 vs. 188±62 min, mean ± SD, p<0.04) with peak values at 5±1 hr. Trop I did not reach peak levels in 8 hr. Area under Curve (AUC) for hFABP and Trop I did not correlate strongly with IS (R^2 =0.57 vs. 0.34). In AMI-R (Fig.), hFABP increased immediately upon reperfusion while Trop I was delayed 20±15 min. (p=0.03). hFABP peak values were reached in 38±15 min after R, Trop. I in 145±15min. (p<0.001). IS by TTC correlated well with 8 hr AUC both for both markers (R^2=0.90). However, hFABP reperfusion peak values (Fig.) showed the highest correlation (R^2=0.98 vs. 0.87). Moreover the intercept value of the trendline nearly coincides with mean baseline hFABP values.



Conclusion: H-FABP release rises significantly faster and correlates better with IS than Trop I in a large animal ischemia-reperfusion model. Maximal hFABP release can be measured within 1 hr upon reperfusion or 5 hr in chronic MI. Taken together, hFABP is an accurate and very fast biomarker for longitudinal in vivo measurement of infarct size in a swine.

TCT-454

A Highly Reproducible and Clinically Relevant Large Animal Model of Myocardial Ischemia and Heart Failure as Determined by MRI Imaging

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Background: Acute myocardial infarction (AMI) and heart failure remain the leading cause of death in United States. Availability of a reproducible large animal model with a large infarction and ejection fraction below 35% is highly desirable for the evaluation of novel myocardial regenerative therapies including cell therapy, injectable matrices, cardiac resynchronization therapy (CRT), and CRT-drug combinations. The goal was to develop a reproducible swine model of myocardial infarction and heart failure with average ejection fraction (EF) below 35%.
Methods: A total of 18 Yucatan miniature pigs underwent minimally invasive closed-chest induction of AMI by percutaneous infusion of collagen gel into the left anterior descending coronary artery (LAD) and side branches under fluoroscopic guidance. Complete occlusion of the LAD and side branches was confirmed and maintained over 2hrs as assessed by coronary angiography. After 3 months, cardiac function was evaluated in surviving pigs (12 of 18) and one naïve uninfarcted Yucatan pig as control using a 1.5T MRI System (MR143 Siemens Magnetom Avanto). Analysis was performed using Circle Cardiovascular Imaging's CMR42 software. Left ventricular volumes at end systole (LVESD) and diastole (LVEDD), ejection fraction (EF), and wall thickness (WT) in the area at risk (AAR) and normal zone (NZ) were calculated.
Results: LVESV and LVEDV in the infarcted pigs were 4- and 2-fold higher, respectively, compared to control. EF was reduced in infarcted pigs compared to control (27.0± 2.3 vs. 59.9%, respectively). WT in AAR and NZ were reduced by 6- and 2-fold, respectively, in infarcted pigs compared to control.

Table: Cardiac MRI evaluation of Uninfarcted and Infarcted pigs 3 months after creation of AMI

	LVESV (ml)	LVEDV (ml)	EF (%)	WT in AAR (%)	WT in NZ (%)
Uninfarcted Control	17.1	42.7	59.9	52.0	77.8
Infarcted	66.8 ± 9.3	90.2 ± 11.3	27.0 ± 2.3	8.9 ± 2.8	40.2 ± 4.2

Conclusion: We have shown that percutaneous infusion of collagen gel into the porcine coronary circulation generates large myocardial infarctions associated with severe cardiac dysfunction and EF below 35%. This highly reproducible model is an important tool for testing of therapies for AMI and congestive heart failure.

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